EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	P.Y. Lum et al.	Attorney Docket No.:	ROSA122057
Application No.:	10/764,420	Art Unit:	1631 / Confirmation No: 6586
Filed:	January 23, 2004	Examiner:	R.S. Negin
Title:	METHODS FOR DETERMINING WHETHER AN AGENT POSSESSES A DEFINED BIOLOGICAL ACTIVITY		

DECLARATION OF DR. YEJUN TAN PURSUANT TO 37 C.F.R. § 1.132

Seattle, Washington 98101

February 6, 2008

TO THE COMMISSIONER FOR PATENTS:

I, Dr. Yejun Tan, declare as follows:

1. I am employed by Rosetta Inpharmatics LLC, Seattle, Washington, as a research fellow, and I am an inventor of the subject matter disclosed and claimed in the above-identified patent application.

2. A copy of my *curriculum vitae* is appended hereto as Exhibit B.

3. I have considered the Office Action dated August 7, 2007, issued in the above-identified application. It is my understanding that the Examiner has rejected claims in the application based on lack of novelty over International Publication No. WO 02/059560 A2 (Castle et al.), and based on obviousness in view of International Publication No. WO 02/059560 A2 (Castle et al.) in further view of Mukherjee et al., *Molecular Endocrinology* 14(9):1425-1433 (2000).

4. I would like to point out to the Examiner that neither the Castle et al. reference nor the Mukherjee et al. reference teach or suggest the claimed method. The Castle et al. method generates a binary outcome and thus could only be used to determine whether a compound is a

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PPAR gamma agonist (with a score of "1"), or is not a PPAR gamma agonist (with a score of "0"). Therefore, in contrast to the claimed invention, the Castle et al. method has no prediction power for the identification and characterization of PPAR gamma *partial* agonists. In contrast to the teachings of Castle et al., as described in the above-identified application, the claimed method is used to determine the *magnitude of response* elicited by a candidate compound and therefore may be used to rank candidate compounds as either partial agonists of PPAR gamma or full agonists of PPAR gamma relative to one or more known partial agonists of PPAR gamma and relative to one or more known full agonists of PPAR gamma (assuming that all compounds were studied at the saturation dose).

5. In order to further illustrate the point that the claimed method may be used to determine the magnitude of response elicited by a candidate agent, I will describe a study that was carried out by myself and my colleagues, using the methods described in the above-identified application. We have conducted microarray experiments to profile PPAR gamma full agonists and PPAR gamma partial agonists in the fully differentiated 3T3-L1 adipocytes. We first selected a gene population of 303 genes from a small training data set that yield an expression pattern that we believe can be used to characterize the general activity of PPAR gamma agonists. We then used the gene expression pattern of the selected 303 genes to characterize and classify other profiled compounds into PPAR gamma full agonists, PPAR gamma partial agonists and not a PPAR gamma agonist. The expression of this 303 gene population that was measured after stimulation with rosiglitazone, a well known PPAR gamma full agonist, was used as a reference. The expression levels of the 303 gene population that was measured in the presence of each of 79 different candidate compounds (at the saturation dose, for example, a dose of 30X EC_{50}) was compared to the expression in the presence of rosiglitazone using a Chi-square fitting approach, (as described in Example 1 of the application) to generate a

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gamma activation index (GAI) score. The GAI comparison score for each of the 79 compounds is shown in the bar chart in **FIGURE 1**.

6. **FIGURE 1** illustrates the gamma activation index (GAI) score for the 79 compounds tested in comparison to the PPAR gamma reference full agonist rosiglitazone (#1 in **FIGURE 1** with a GAI score of 1.0), and in comparison to the negative controls (LXR agonist #78, PPAR alpha agonist #79, and vehicle only control #80, each with a GAI score below 0.1).

The results shown in the bar graph of **FIGURE 1** allow one to rank the 79 candidate compounds relative to one another, relative to one or more known partial agonists of PPAR gamma, and relative to one or more known full agonists of PPAR gamma. For example, the compounds with the comparison scores above 0.9 (e.g. candidate compounds #1 to #7 shown in FIGURE 1) may be categorized as PPAR gamma full agonists, while the compounds with comparison scores from 0.2 to 0.85 (e.g. candidate compounds #8 to #77 shown in FIGURE 1) may be categorized as partial PPAR gamma agonists. Compounds below 0.1 are not PPAR gamma agonists. Therefore, the claimed method can differentiate a PPAR gamma partial agonist with a GAI score of 0.25 from another PPAR gamma partial agonist with a GAI score of 0.75. The ability to rank the candidate compounds in terms of magnitude of response is useful for selection of the optimum lead candidate to proceed to clinical trials. In contrast to the claimed method, the method described in Castle et al. does not allow one to identify partial agonists or rank compounds in terms of magnitude of response relative to a reference.

7. It is my understanding that the Examiner has cited the Mukherjee et al., *Molecular Endocrinology* 14(9):1425-1433 (2000) reference as disclosing that a *correlation* exists between PPAR gamma affinity and the "minimum effective dose" required to lower glucose levels in diabetic rodent models. In this regard, I would like to point out that the teachings of Mukherjee et al., which disclose a correlation approach, do not teach or suggest the comparison methods of

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the present invention, which provides a magnitude of response of an agent and are typically carried out using a chi-square fitting analysis. A correlation coefficient (such as Pearson correlation) measures the linear association of one variable compared with another variable (i.e. how far all the data points deviate from the best fitted line). In contrast, the claimed invention is used to determine the *magnitude of response* elicited by a candidate compound, for example, by using a chi-square fitting which measures how large in magnitude one variable differs compared to another variable (i.e. the slope between the best fitting line and the x-axis). Therefore, neither the teachings of Mukherjee nor Castle et al. teach or suggest the claimed invention.

8. The following hypothetical example is provided to further illustrate the difference between the methods of the claimed invention (i.e. using a chi-square fitting approach) and the correlation approach taught in Mukherjee. **FIGURE 2** shows a comparison of the expression of 4 hypothetical genes in response to a full agonist (F) or in response to two partial agonists (P1) and (P2). The upper line in **FIGURE 2** shows a comparison between P1 and F, with a correlation coefficient of 1.0, and a chi-square fitting result of 0.75. The lower line in **FIGURE 2** shows a comparison result between P2 and F, with a correlation coefficient of 1.0, and a chi-square fitting result of 0.3. Therefore, as shown in **FIGURE 2**, the correlation coefficient for P1 versus F and P2 versus F are both equal to 1.0. In contrast, using a chi-square fitting method of comparison allows a ranking to be established between P1 (0.75) and P2 (0.3), in accordance with the method of the present invention.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code,

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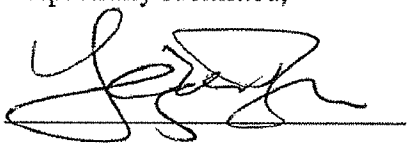
and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,



Dr. Yejun Tan, Ph.D

Date: 02/06/2008

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Suite 2800
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206.682.8100

FIGURE 1

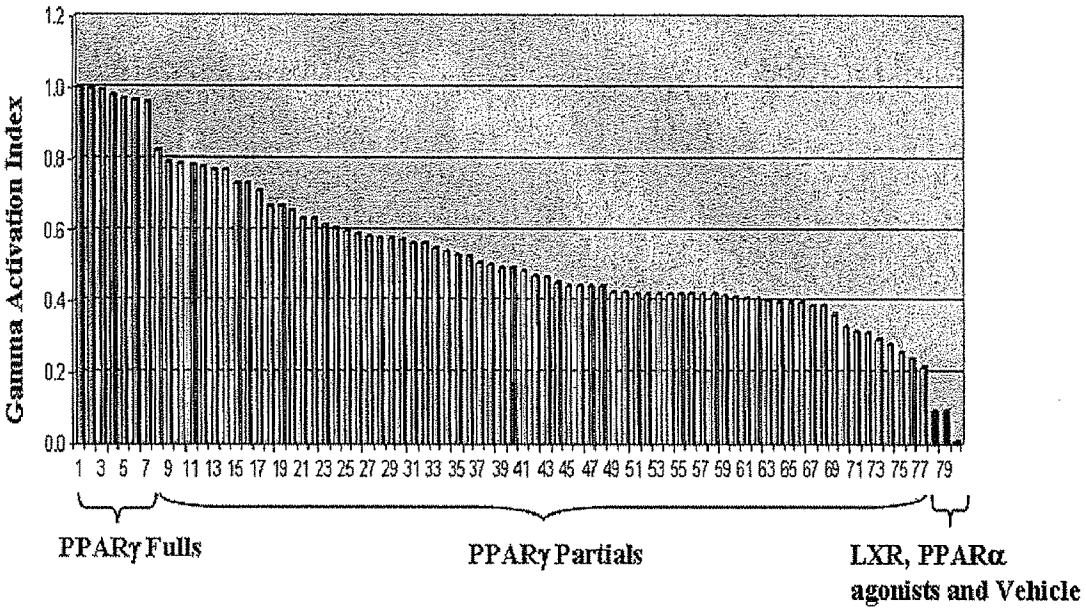

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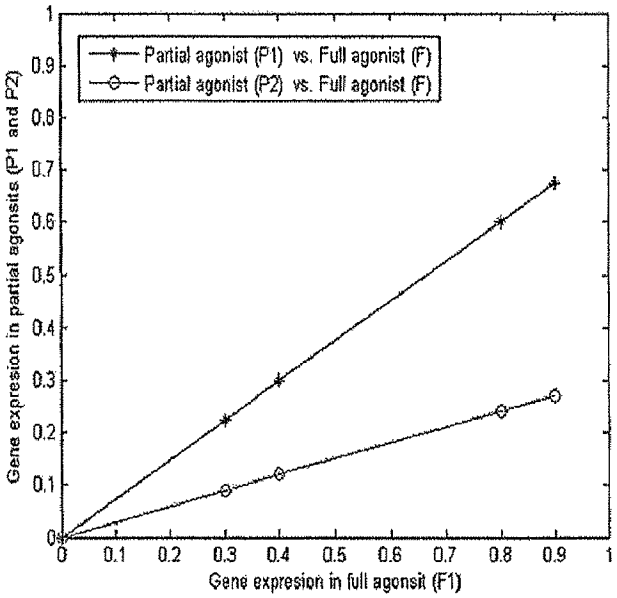
FIGURE 2



Comparison between P1 and F
Correlation coefficients = 1;
Chi-square fitting result = 0.75

Comparison between P2 and F
Correlation coefficients = 1;
Chi-square fitting result = 0.3

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

EXHIBIT B

Yejun (Eugene) Tan, Ph.D./MBA

Address: 401 Terry Ave N, Seattle, WA 98109
Company: Rosetta Inpharmatics, LLC./Merck & Co., Inc.
E-mail: eugene_tan2@merck.com
Fax: (206)802-6411
Telephone: (206)802-6315 (w), (425)318-2948 (c)

Education:

1992 - 1999 **Ph.D. in Biochemistry**
University of Illinois at Chicago
Chicago, Illinois 60607

1997 - 1999 **Master of Business Administration**
University of Illinois at Chicago
Chicago, Illinois 60607

1997 - 1999 **M.S. in Management Information Systems**
University of Illinois at Chicago
Chicago, Illinois 60607

1986 - 1991 **B.S. in Biology**
University of Science & Technology of China
Hefei, Anhui, P.R.China

Career History:

2005 - present
Research Fellow, Rosetta Inpharmatics,LLC./Merck & Co.,Inc.
Conducted data analysis in the transcriptomic and proteomic profiling to assist the discovery and development of the next generation anti-diabetic medicines.

2001 - 2005
Senior Research Scientist/Senior Data Analyst, Rosetta Inpharmatics,LLC./Merck & Co.,Inc.
Conducted data analysis in the transcriptomic profiling to assist the discovery and development of novel compounds with improved therapeutic index compared with PPAR gamma full agonists.

2000 - 2001
Data Analyst, Rosetta Inpharmatics,Inc.
Implemented and tested statistical algorithms and the Combiner Services for the Rosetta Resolver™ System.

Publication and Patent:

Available Upon Request